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GlaxoSmithKline

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**GlaxoSmithKline
Research & Development**
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

Tel. 919 483 2100
www.gsk.com

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

**Re: Docket Nos. 2004P-0290 & 2004P-0488;
Supplement to Citizen Petitions**

Dear Sir or Madam:

The undersigned, on behalf of GlaxoSmithKline (GSK), submits this supplement to the above-referenced citizen petitions, filed by the Food and Drug Administration (FDA) on July 8 and November 5, 2004. This supplement addresses the Draft Guidance for Industry: *ANDAs: Pharmaceutical Solid Polymorphism* (Dec. 2004) (Draft Guidance). See 69 FR 75987 (Dec. 20, 2004).

The recently released draft guidance proposes a "framework for making regulatory decisions on drug substance sameness" for drugs that exist in polymorphic forms. *Id.* at 75988. It also includes a series of "decision trees" to advise generic drug sponsors when polymorphic forms must be monitored and carefully controlled. *Id.* The draft guidance, when finalized, will represent FDA's "current thinking" on pharmaceutical solid polymorphism. *Id.* At this time, the issues described in the draft guidance, including issues related to drug substance sameness, remain unresolved and subject to comment. See 21 CFR 10.115.

GSK intends to comment on the draft guidance within the 90-day period provided by FDA and will copy its comment to the above-reference dockets. Because of its relevance to the pending petitions, however, GSK is supplementing its petitions to note the following deficiencies in the draft guidance.

First, the draft guidance fails to address the impact that polymorphic forms have on topical dosage forms, such as creams and ointments. The draft guidance acknowledges that different polymorphic forms may have different melting points, reactivity, solubility, dissolution rates, optical and mechanical properties, vapor pressure, and density. See Draft Guidance at lines 73-75. The draft guidance omits, however, any discussion of how such differences may impact the relative performance of proposed generic topical drug products. Only the rate limiting factors of dissolution and solubility, as applied to oral dosage forms, are discussed in the draft guidance. See *id.* at lines 102-14.

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Second, the discussion of the United States Pharmacopeia's (USP) standards of identity fails to recognize that USP monographs invariably include spectrophotometric identification tests, such as tests of infrared and ultraviolet absorption. *See id.* at lines 179-82. Infrared tests in particular allow for the detection of polymorphic forms and, where necessary, USP monographs specifically control for solid state structure. Also, as discussed in the earlier of GSK's petitions, the agency has yet to articulate how it will establish standards of identity – including standards with respect to solid state structure – in the absence of a USP monograph. *See* Citizen Petition, Docket No. 2004P-0290 (July 7, 2004) at 11-13. The draft guidance fails to address this issue.

Third, GSK disagrees with the categorical statement in the draft guidance that “differences in drug substance polymorphic forms do not render drug substances different active ingredients.” Draft Guidance at lines 190-92. According to the preamble discussion referenced by FDA, polymorphic forms – including crystalline structures – may well be relevant to the issue of “sameness” of drug substance for purposes of section 505(j) of the Food, Drug, and Cosmetic Act. *See id.* at lines 185-90. As FDA explained in the preamble:

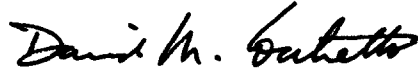
Under the statute, an ANDA applicant must show that its active ingredient is the same as that in the reference listed drug (21 USC 355(j)(2)(A)(ii)). FDA will consider an active ingredient to be the same as that of the reference listed drug if it meets the same standards for identity. In most cases, these standards are described in the [USP]. However, in some cases, FDA may prescribe additional standards that are material to the ingredient's sameness. *For example, for some drug products, standards for crystalline structure or stereoisomeric mixture may be required.* Should questions arise, an applicant should contact the Office of Generic Drugs to determine what information would be necessary to demonstrate that its active ingredient is the same as that in the reference listed drug.

57 FR 17950, 17959 (April 28, 1992) (emphasis added). This passage, relied upon by FDA in the draft guidance, specifically contemplates that internal solid state structure may bear on drug substance identity on a case-specific basis. For example, as demonstrated in GSK's petitions, crystalline structure is relevant to the identity of mupirocin calcium.

We note these deficiencies to ensure that the concepts outlined in the draft guidance are not applied prematurely to the above-referenced petitions, until GSK and other members of the public have been provided an opportunity to study the draft guidance and provide thorough comments.

Thank you for your consideration. As stated above, GSK intends to comment on the draft guidance within 90 days, and will copy its comment to the above-referenced dockets.

Respectfully submitted,



David M. Cocchetto, Ph.D.
Vice President
Antiviral/Antibacterial Regulatory Affairs

cc: David M. Fox
Brian R. McCormick
Hogan & Hartson L.L.P.